201-14164

"Deford, Connie (CL)" <CLDeford@dow.com> on 12/22/2002 02:08:40 PM

To: "'chem.rtk@epa.gov'" <oppt.ncic@epa.gov,>
cc:

Subject: RE: HPV SUBMISSION - DIPHENYL OXIDE

Sir: Enclosed are the HPV documents for Diphenyl Oxide, which we are submitting on behalf of Solutia, Inc. and The Dow Chemical Company. Please have these documents posted on the EPA website for HPV chemicals. Attached is a cover letter, test plan and the IUCLID document. This information has been added to the US HPV Chemical Tracking System at http://www.hpvchallenge.com. Please let us know if you have any questions.

<<Dow HPV DPO Cover letter.doc>> <<HPV DPO Test Plan pdf.pdf>> <<DPO IUCLID Solutia Dow pdf.pdf>>

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Industrial Chemicals
Global EH&S Product Leader
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Fax: (989-636-9899)
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Dow HPV DPO Cover lett


HPV DPO Test Plan pd


DPO IUCLID Solutia Dow p

201-14164

The Dow Chemical Company
Midland, Michigan 48674

2020 Dow Center
December 20, 2002

Ms. Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know – HPV Challenge Program

Dear Ms. Whitman:

On behalf of Solutia, Inc. and The Dow Chemical Company, I am pleased to submit the Test Plan and Robust Summaries in IUCLID format for Diphenyl Oxide (Cas No.: 101-84-8). As requested, the test plan has also been posted onto the U.S. HPV Chemical Tracking System. All documents are Adobe Acrobat (pdf) files.

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the following address:

Ms. Connie L. Deford
The Dow Chemical Company
Larkin Laboratory
1691 North Swede
Midland, MI 48674
email: cldeford@dow.com
phone: (989) 636-6978

Sincerely,

Connie L. Deford
Global Environment, Health & Safety Manager

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

DIPHENYLOXIDE

CAS NO. 101-84-8

Prepared by:

Solutia, Inc. Registration No.
575 Maryville Centre Drive,
St. Louis, Missouri 63141

The Dow Chemical Company
Midland, Michigan 48674

EXECUTIVE SUMMARY

Solutia Inc. and The Dow Chemical Company voluntarily submit the following screening information data and Test Plan covering the chemical, Diphenyl Oxide, also known as Diphenyl Ether and DPO (CAS No. 101-84-8), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with DPO. Use of key studies or estimation models available from data already developed provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing.

TABLE OF CONTENTS

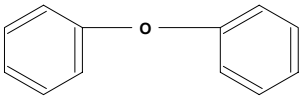
TEST PLAN FOR DIPHENYLOXIDE (DPO)

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. (Solutia) and The Dow Chemical Company (Dow) has committed to voluntarily compile basic screening data on Diphenyl Oxide or DPO. The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of DPO, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed by or on behalf of Solutia or Dow or found in the published scientific literature and fulfills Solutia's and Dow's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of DPO and associated nomenclature.



Diphenyl Oxide

CAS No. : 101-84-8
Synonyms: diphenyl ether; Benzene, 1,1'-oxybis-; DPO

B. Manufacturing & Use

DPO is manufactured by two US producers, Solutia and Dow; each operating a single manufacturing site. The manufacturing operations are closed, continuous processes. Only a few employees are involved in its manufacture at each site and have minimal potential for skin or airborne exposure, which occur chiefly during material transfer operations. Due to the acute hazards and occupational exposure limit of 1 ppm, specific manufacturing procedures and practices have been established to minimize the exposure potential to DPO.

Diphenyl oxide is sold primarily to industrial customers, both in the U.S. and in the rest of the world, for use either as a heat transfer fluid (blended with biphenyl) or as a chemically reacted intermediate in the production of flame retardants, surfactants, textile dye labeling and in coating applications. Both in DPO's use as a chemical intermediate

and as a heat transfer fluid, DPO is processed and utilized exclusively in closed systems. Occupational exposure during processing or use would primarily occur during material transfer or, in the unlikely event, that there is an unplanned event. Loss to the atmosphere or from non-POTW aqueous streams during manufacturing or processing is minimal. Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either:
1) Internal studies conducted by/or for Solutia (or its predecessor Monsanto Co.),
2) Internal studies conducted by/or for Dow
3) Studies that have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or
4) Studies that were estimated using environmental models accepted by the US EPA (1999b) for such purposes.

This assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with DPO. The data used to support this program include those Endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Valid without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Valid with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3. Not Valid – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – This designation not used in this Dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. Additional studies have been identified during our literature search on the referenced HPV endpoints but have not been summarized in this Dossier. The reader is referred to one additional data compendium, which also summarize available data on the physical-chemical properties, ecotoxicity, environmental fate and health effects of diphenyl oxide. This is the European Chemical Bureau (ECB) IUCLID Dossier for Diphenyl Oxide (2000).

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Hence, no further testing for any of the HPV Endpoints is deemed necessary (Table 1).

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, and Water Solubility) were obtained from reputable, universally accepted reference guides. These endpoints have been classified as "2-Valid with restrictions".
The Partition Coefficient was measured using OECD Guideline 107 Method and estimated using an EPA recommended model; it has been classified as "1-Valid without restriction".

Environmental Fate values for Transport (Fugacity) were obtained using a computer estimation –modeling programs (Fugacity Based Environmental Equilibrium Partitioning Model, Level I, 1999) and (EPIWIN Level III Fugacity Model, 2002), recommended by EPA; they have been classified as "2-Valid with restrictions". Biodegradation data was obtained using methodology patterned after JAOCS 42:986 and JAOCS 45:432 and classified as "2-Valid with restrictions". Photodegradation data was estimated using EPA recommended model and was considered "2-Valid with restrictions". In keeping with OECD SIDS guidance, no testing for Stability in Water is planned with DPO as it is generally recognized as "stable" in aqueous solutions. Supplemental data to evaluate Bioaccumulation in fish used a protocol consistent with OECD Guidance and was considered "2-Valid with restrictions".

Ecotoxicity Endpoints for Acute Invertebrate Toxicity and Acute Fish Toxicity were met with studies conducted with methodology that was consistent with OECD test guidance. The Acute Plant Toxicity study was conducted according to a regulatory-recommended study design. Studies supporting the Acute Invertebrate, Acute Fish Toxicity and Acute Toxicity to Plants Endpoints were designated a reliability level of "2-Valid with restrictions".

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing, Developmental Toxicity and

Reproductive Toxicity) have all been filled by way of tests which either conformed directly with OECD test guidance or followed test designs similar to OECD guidance. The Acute Toxicity Endpoint was supported by a study, which was consistent with OECD guideline 401 and GLPs, and was considered "2- Valid with restrictions". The Repeated Dose Toxicity Endpoint was conducted with methodology consistent with an OECD guideline 408 study in accordance with GLPs. It also was codified as "1- Valid without restriction". The Ames test followed a study design equivalent to OECD guideline # 471 and the chromosomal aberration study was conducted under OECD guideline # 473 parameters. Thus, the Ames test was categorized as "2- Valid with restrictions" while the chromosomal aberration study was classified as "1- Valid without restrictions"

A Developmental Toxicity Study fulfills the HPV requirements for the Mammalian Toxicity Endpoint. This study was conducted to meet OECD Guideline 414 in design and is compliant with GLPs. It has been classified as "1- Valid without restriction".

Based on previous guidance from EPA and the OECD SIDS program, the endpoint of Reproductive Toxicity has been adequately met by (a) histopathologic data reporting the absence of toxicologic effects for the male and female reproductive/endocrine organs examined in a recent GLP OECD 408 Subchronic Toxicity study, and (b) availability of a GLP OECD 414 Developmental Toxicity study.

A tabular depiction of data availability and testing recommendations for Diphenyl Oxide (DPO) can be found on the following page.

Table 1. Test Plan Matrix for Diphenyl Oxide

	Info. Avail.?	OECD?	GLP?	Other Study?	Estimat. Method?	Accept-Able ?	Testing Recomm.?
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	N	-	Y	N
Boiling Point	Y	R	N	N	-	Y	N
Vapor Pressure	Y	R	N	N	-	Y	N
Partition Coefficient	Y	R	N	Y	-	Y	N
Water Solubility	Y	R	N	Y	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	N	N	Y	Y	N
Biodegradation	Y	N	N	Y	-	S	-
Transport between Environmental Compartments (Fugacity)	Y	N	N	N	Y	Y	N
Bioaccumulation	Y	N	N	N	-	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	Y	Y	-	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	N	Y	Y	-	Y	N
Acute Toxicity to Aquatic Plants	Y	N	Y	Y	-	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	N	N	Y	-	Y	N
Repeated Dose Toxicity	Y	N	Y	Y	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	N	N	Y	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	Y	N	-	Y	N
Developmental Toxicity	Y	Y	Y	N	-	Y	N
Reproductive Toxicity	Y	Y	Y	N	-	Y	N

Y = Yes; N = No; S = Supplemental, not required under HPV; R = Reputable Reference; - = Not applicable

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of Diphenyl Oxide

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 20 ^{o}C)	Water Solubility (ppm)	Partition Coefficient (Log Kow)
Diphenyl Oxide CAS No. 101-84-8	257-259	28	2.67 Pa or 0.0267 hPa	21 @ 25 ^{o}C.	4.2

All HPV Endpoints for Chemical/Physical Properties have been completed with reliable information and taken from either primary or reputable textbook references (Table 2). The values, which are included in the Robust Summary section of this Dossier, have been classified as "2-Valid with restrictions". Additional Chemical/Physical property values can also be found in the ECB IUCLID Dossier for DPO (2000).

In summary, these data indicate that DPO is a white crystalline solid or colorless liquid, depending upon temperature. The melting point of DPO is 28 ^{o}C. DPO is moderately soluble in water. The magnitude of the octanol:water partition coefficient indicates a moderate bioconcentration potential for DPO. However, the measured bioconcentration factor for diphenyl oxide in rainbow trout has been reported to be 196, indicating significant metabolic clearance of the compound from the fish.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with DPO. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

Extensive reviews and study citations in the Environmental studies area have been published on DPO, and are summarized in the ECB IUCLID Dossier (2000) for DPO. Key studies have been selected for this Dossier, which fairly depict the consensus conclusion/values for each of the HPV Endpoints listed (Table 3), and are summarized in the Robust Summary section of this Dossier. The Biodegradability study selected employs methodology that is well established for determination of this HPV Endpoint; it has been designated as "2-Valid with restrictions". Photochemical degradation of DPO

was estimated using the Atmospheric Oxidation Program recommended for use by EPA. (AOP, 1997, Syracuse Research Corporation). Estimation of Transport (Fugacity) was made using an EPA-accepted estimation model (Fugacity Based Environmental Equilibrium Partitioning Model, Level I 1997) and (EPIWIN Level III Fugacity Model, 2002). These values have been designated as "2-Valid with restrictions". No experimental data could be located to define the Stability in Water (Hydrolysis) of DPO, nor could a value be calculated using EPIWIN (2002), as this chemical has only aromatic and ether functional groups; both of these groupings are listed in Lyman et al (1990) as Generally Resistant to Hydrolysis. Thus, "[t]esting for Stability in Water is not needed for substances generally recognized to have molecular structures or possess only functional groups that are generally known to be resistant to hydrolysis " (OECD, 2002). An overview of the known qualities of the environmental properties of DPO is provided below.

The environmental fate of DPO can be summarized as follows. Based on fugacity modeling, DPO released into the environment will partition primarily between air, water and soil (Table 3 - Fugacity). Upon release to the air, DPO will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. The estimated half-life in air is approximately 1 day (Table 3 – Photodegradation). DPO is expected to biodegrade in a wastewater treatment plant (Table 3 – Biodegradation). Substantial biodegradation of DPO in biochemical oxygen demand (BOD) tests (ECB IUCLID, 2000) indicates that, upon release to surface waters and soil, biodegradation of DPO will occur. DPO is not susceptible to hydrolysis. Based on the octanol/water partition coefficient, DPO has a moderate potential to bioconcentrate in aquatic species. However, the measured bioconcentration factor for diphenyl oxide in rainbow trout has been reported to be 196, indicating significant metabolic clearance of the compound from the fish.

Table 3. Environmental Fate and Biodegradation Parameters for Diphenyloxide

Chemical	Biodegradation Rate	Stability in Water	Fugacity (%) Level III	Photodegrad. Rate
DPO CAS No:101-84-8	51-94% primary biodegradation after 7 days in activated sludge	Stable	Air – 4.47 Water – 28.9 Soil – 63.7 Sediment – 2.87	50% after 1.1 day .

Conclusion – Adequate studies following either OECD or EPA test guidance are available to provide needed information regarding the Biodegradation and Photodegradation of DPO. Information on Transport (Fugacity) was completed using the Fugacity Based Environmental Equilibrium Partitioning Model Level I and EPIWIN Level III Fugacity Model, accepted estimation-modeling programs. No additional data development is warranted for these HPV Endpoints.

C. Aquatic Toxicity

The aquatic toxicity of DPO has been extensively reviewed (ECB IUCLID, 2000) and contains numerous acute toxicity studies on algae, invertebrates and fish. The key studies selected for development of Robust Summaries are reported in Table 4 and depict the level of toxicity generally observed for these Endpoints within the overall dataset.

Both the Acute Invertebrate Toxicity and Acute Fish Toxicity were met with studies conducted with methodology that was consistent with OECD test guidance and under GLPs. The Acute Plant Toxicity study was conducted according to a regulatory-recommended study design under GLPs. Studies supporting the Acute Invertebrate, Acute Fish Toxicity and Acute Toxicity to Plants Endpoints were designated a reliability level of "2-Valid with restrictions".

Table 4. Aquatic toxicity parameters for Diphenyl Oxide (DPO)

Chemical	Fish LC 50 (mg/L)	Invertebrate EC50 (mg/L)	Algae EC50 (mg/L)
Diphenyl Oxide CAS No.101-84-8	(rainbow trout -96 hr) 4.2	(Daphnia-48 hr) 1.7	(Selenastrum capricornutum 96-hrs) 2.5

DPO is considered to be only "moderately toxic", according to EPA categorization guidance, toward these and other aquatic species following acute testing. Based on the pattern and release scenarios envisioned, DPO is expected to present a negligible risk to aquatic organisms.

Conclusion – Adequate studies which are consistent with internationally accepted test guidelines are available on all 3 Aquatic Toxicity Endpoints to assess the acute aquatic toxic hazards associated with DPO. Therefore, no additional data development is needed for these HPV Endpoints.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

Table 5. Mammalian Toxicity of Diphenyl Oxide (DPO)

Chemical Name/ CAS no.	Acute Toxicity	Repeat Dose Toxicity	Reproductive Toxicity	Developmental Toxicity	Mutagenicity –In Vitro	
	Oral LD50 (rat)	90-day			Point Mutations (Ames)	Chrom. Aberr. (CHO cells)
Diphenyl oxide 101-84-8	2450 mg/kg	(oral-rat) NOAEL >5000 ppm in diet	Histopathologic exam of male and female reproductive/ endocrine organs in subchronic OECD 408 study, and availability of OECD 414 study	(gavage-rat) NOAEL for Maternal toxicity 50 mg/kg bw NOAEL for developmental toxicity 500 mg/kg bw	Neg.- All strains (TA98, TA100, TA1535, TA1537) +/- S9	Neg. + / - S9

1.0 Acute Toxicity

An acute toxicity study by the oral route of exposure has been conducted as summarized in Table 5. This study was conducted prior to, but consistent with GLPs (finalized in 1979) and used a study design consistent with OECD Test Guidelines 401; it is considered "2- Valid with restrictions". The acute rat oral toxicity study has been chosen as the key study to fulfill this HPV Endpoint.

DPO is considered to be of low toxicity after acute oral exposure to rats. Additional acute toxicity values in animals can be found listed in the compendium report cited above.

Conclusion – A quality study, consistent with OECD/GLP guidance, is available to assess the Acute hazards associated with DPO. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

DPO has been adequately tested by the oral route of exposure to define its Repeated Dose Toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route reported in 1990. This study was conducted using a study design consistent with OECD Test Guideline 408, and under

GLP auspices and is considered "1- Valid without restriction". Groups of 20 male and 20 female rats received diets containing concentrations of 0, 200, 1000 and 5000 ppm DPO for 13 weeks. Ten rats/sex/dose were terminated at the end of the 13-week dosing period. The remaining 10 rats/sex/dose were maintained on basal diet for a 4 week post-treatment group. A full complement of clinical parameters was evaluated. Histopathologic examination was conducted on a full complement of tissues, including the male and female reproductive and endocrine organs. Body Weight gain and Food Consumption were decreased in the 5000 ppm males and females and in the 1000 ppm females; these changes were secondarily attributed to the unpalatability of the DPO test diets, as evidenced by the increases in Body Weight and Food Consumption during the post-treatment period. No adverse toxicologic effects were attributed to the DPO, and the NOAEL was determined to be 5000 ppm in the diet, equating to 301 mg/kg/day for males and 335 mg/kg/day for females. A summary of this study is found in the Robust Summary section of this Dossier.

Conclusion - Thus, the Repeated Dose HPV Endpoint for DPO has been fulfilled with a 90-Day Subchronic study in rats deemed "1- Valid without restriction". No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

3.1 Mutagenicity Testing (Ames test)

DPO has been extensively tested in the standard Ames assay for point mutations (ECB IUCLID, 2000). DPO elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. A representative study has been summarized in the Robust Summary section of this Dossier and its results are referenced in Table 5. Its design and documentation are such that it is considered consistent with OECD guideline 471 and thus is "2- Valid with restrictions" for this assessment.

Thus, it is concluded that adequate testing of sufficient quality has been performed on DPO to evaluate the Ames Test (Point Mutation) HPV Endpoint; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

DPO has been tested in an in vitro chromosomal aberration test; no significant increases in structural aberrations per cell at any treatment concentration were observed. A Robust Summary has been prepared for this study and its results are referenced in Table 5. It was conducted using GLPs and meets OECD guideline 473 parameters; it is considered "1-Valid without restriction".

The HPV Chromosomal Aberration Endpoint for testing of DPO has been fulfilled with adequately conducted and documented studies and no further testing is needed.

4.0 Developmental Toxicity

A Developmental Toxicity study of DPO has been conducted using oral gavage (Table 5) and summarized in Dossier section VI - Robust Summaries. It was conducted under GLPs and meets OECD 414 Testing Guidelines. Based on general acknowledgement of its scientific and regulatory acceptability, it has been judged as "1- Valid without restriction" for purposes of this assessment. The test material was administered by oral gavage in corn oil to groups of 24 mated female rats at 0, 50, 200 and 500 mg/kg/d. Single oral daily dosages were administered at a volume of 5 ml/kg by gavage, on gestation days 6-15. Maternal toxicity was noted at the two higher dose levels of 500 and 200 mg/kg/day, and included decreases in Body Weight gain and Food Consumption, excessive salivation, alopecia and staining of the hair coat in the ano-genital region; deaths of 2 high dose rats were considered related to the treatment. No effects observed on fetal resorptions, fetal viability, postimplantation loss or total implantations. Mean litter weights in treated and control groups were similar. No significant increases were observed in incidence of fetal malformations or variations at any treatment level. The NOAEL for maternal toxicity was >/= 50 mg/kg/d and the NOAEL for teratogenicity was >/= 500 mg/kg/d, the highest dosage tested.

5.0 Reproductive Toxicity

The Reproductive Toxicity endpoint for DPO under the HPV program is considered adequately met by (a) availability of a recent comprehensive GLP OECD 408 subchronic toxicity study that included histopathologic examination that revealed no adverse effects on the male and female reproductive organs (including testes, epididymides, prostate, seminal vesicles, uterus, ovaries, vagina, mammary gland, pituitary, thyroid, parathyroid and adrenals, and (b) availability of a GLP Developmental Toxicity study (OECD 414). The EPA HPV Guidance Document entitled 'Determining the Adequacy of Data' cites the OECD SIDS position wherein if there is an existing, adequate 90-day repeat-dose study that demonstrates no effects on reproductive organs (particularly the testes), than a Developmental Toxicity study (e.g., OECD 414) can be considered as an adequate test for information on reproduction/developmental effects. These criteria have been adequately met by the data presently available on DPO.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled with conduct of a Developmental rat study and a 13-week Subchronic Toxicity study which followed OECD testing guidance and was conducted under GLPs. As no effects on male or female gonads were observed in the Subchronic study, a combination of these two studies has been used to fulfill this HPV requirement, per US EPA HPV guidance. Thus, no further testing for this HPV Endpoint is required.

V. REFERENCES

AOP, v.1.8. 1997. Syracuse Research Corporation, Syracuse NY.

EPIWIN, 2002. Version 3.10, Syracuse Research Corporation, Syracuse, New York.

European Chemical Bureau (ECB). 2000. IUCLID Dossier for Diphenyl Oxide.

Fugacity Based Environmental Equilibrium Partitioning Model. Level 1. Version 2.11. 1999. Trent University.

Klimisch, H.-J., Andreae, M. and Tillman, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Lyman, W.J., Reehl, W.F. and Rosenblatt, D.H. 1990. *Handbook of Chemical Property Estimation Methods. Environmental Behaviour of Organic Compounds.* American Chemical Society, Washington, DC.

OECD, 2002. Organization of Economic Cooperation and Development. Existing Chemicals Programme, SIDS Dossier on HPV Chemicals (latest draft-May, 2002).

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide). Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are appended

I U C L I D

Data Set

Existing Chemical	:	ID: 101-84-8
CAS No.	:	101-84-8
EINECS Name	:	diphenyl ether
EINECS No.	:	202-981-2
TSCA Name	:	Benzene, 1,1'-oxybis-
Molecular Formula	:	C12H10O

Producer Related Part

Company	:	Solutia Inc./Dow Chemcial Co.
Creation date	:	25.09.2000

Substance Related Part

Company	:	Solutia Inc./ Dow Chemical Co.
Creation date	:	25.09.2000
Memo	:	
Printing date	:	26.11.2002
Revision date	:	
Date of last Update	:	26.11.2002
Number of Pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	28 ° C
Sublimation	:	
Method	:	other
Year	:	1983
GLP	:	no data
Test substance	:	other TS
Method	:	not referenced
Test substance	:	Diphenyl oxide
Reliability	:	(2) valid with restrictions Citation in reputable, universally accepted reference guide.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (14)

2.2 BOILING POINT

Value	:	257 - 259 ° C at
Decomposition	:	
Method	:	other
Year	:	1983
GLP	:	no data
Test substance	:	other TS
Method	:	not referenced
Test substance	:	Diphenyl oxide
Reliability	:	(2) valid with restrictions Citation in reputable, universally accepted reference guide.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (14)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	.02 mm Hg at 25° C ; 0.12 mm Hg at 30 deg. C.
Decomposition	:	
Method		other (measured)
Year	:	1983
GLP	:	no data
Test substance	:	other TS
Method	:	not referenced
Result	:	
Test substance	:	Diphenyl oxide
Reliability	:	(2) valid with restrictions Citation in reputable, universally accepted reference guide.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (14)

2.5 PARTITION COEFFICIENT

Log pow	:	4.2 at 20° C
Method		OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year	:	1980
GLP	:	no data
Test substance	:	other TS
Method	:	Additional estimated value derived for comparison using KOWWIN (1997), Syracuse Research Corp., Syracuse, NY
Test substance	:	Diphenyl oxide
Reliability	:	(1) valid without restriction
Remark		Measured value obtained from study design similar to OECD 107. This value is consistent with estimated log Pow value of 4.1 using Octanol-Water Partition Coefficient Program KOWWIN from Syracuse Research Corporation, 1997. Log Kow values are often used to predict the potential for a compound to bioconcentrate in aquatic organisms. The measured bioconcentration factor for diphenyl oxide in rainbow trout has been reported to be 196, indicating significant metabolic clearance of the compound from the fish [Neely, W. B., Branson, D. R., and Blau, G. E. 1974. Environ. Sci. Technol., 8:1113-1115; these data are also found in Dow report WCL-73015: DR Branson, NH Litchfield, and HC Alexander. 1973. Bioconcentration of diphenyl oxide in trout. DR-0000-7307-099-WCL73015].
Flag	:	Critical study for SIDS endpoint

25.11.2002 (2)

2.6.1 WATER SOLUBILITY

Value	:	21 ppm at 25 ° C
Qualitative	:	
Pka	:	
PH	:	
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	other TS
Method	:	not referenced
Test substance	:	Diphenyl oxide
Reliability	:	(2) valid with restrictions Citation is from reputable, universally accepted reference guide and also consistent with estimated value of 16 ppm derived from structure-activity relationships from the Water Solubility Log Kow Program from Syracuse Research Corp., 1997.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (14)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Indirect photolysis

Sensitizer	:	OH
Conc. of sens.	:	1600000 molecule/cm3
Rate constant	:	.0000000000098 cm3/(molecule*sec)
Degradation	:	50 % after 1.1 day
Deg. Product	:	
Method	:	other (calculated)
Year	:	1997
GLP	:	
Test substance	:	other TS
Method	:	Estimation using the AOP model (Atmospheric Oxidation Program), version 1.9. Syracuse Research Corporation, 1997.
Reliability	:	(2) valid with restrictions Computer estimation model recommended for use by US EPA.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (1)

3.1.2 STABILITY IN WATER

Value	:	Diphenyl oxide not susceptible to hydrolysis under environmental conditions
Remark	:	Compound does not contain hydrolyzable functional groups. Lyman, W. J., Reehl, W. F., Rosenblatt, D. H. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Company, New York, NY. Estimation program cannot predict hydrolysis rate due to lack of hydrolyzable groups [Syracuse Research Corporation; Aqueous Hydrolysis Rate Program HYDROWIN; 1996].
Method		
Year	:	
GLP	:	
Test substance	:	
Method	:	
Result	:	
Test substance	:	Diphenyl oxide
Reliability	:	(2) valid with restrictions Citation in reputable, universally accepted reference guide.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (14)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	Fugacity model level I (version 2.11)
Media	:	other

Method : Input parameters
Molecular mass (g/mol) = 170.2
Temperature (°C) = 25
Log Kow = 4.2
Water Solubility (g/m^3) = 21
Vapor Pressure (Pa) = 2.67
Henry's Law Constant (Pa.m^3/mol) = 21.6
Melting Point (°C) = 28

Results
Distribution of DPO:

22.1% to Air	0.004% to Biota (Fish)
5.1% to Water	0.05% to Suspended Sediment in Water
1.6% to Sediment	<0.001% to Aerosols
71.2% to Soil	

Year : 2002
Method : Estimation based on fugacity calculations
Reliability : (2) valid with restrictions
Flag : Supplemental study for SIDS endpoint
26.11.2002

Type : fugacity model level III
Media : other
Air (level I) : 4.47
Water (level I) : 28.9
Soil (level I) : 63.7
Biota (level II / III) :
Soil (level II / III) : 2.87
Method : other
Year : 2002
Method : Calculated according to MacKay, using EPIWIN 3.05, EQC Level III. Assumed emissions (1000 kg/hr) to air, water and soil compartments using measured values as available from this reference document. Last soil entry included data estimate for sediments.

Results

```
Level III Fugacity Model (Full-Output):
=======================================
  Chem Name    : Diphenyl oxide
  Molecular Wt: 170.21
  Henry's LC   : 0.000279 atm-m3/mole (Henry database)
  Vapor Press : 0.02 mm Hg  (user-entered)
  Liquid VP    : 0.0214 mm Hg  (super-cooled)
  Melting Pt   : 28 deg C (user-entered)
  Log Kow      : 4.2  (user-entered)
  Soil Koc     : 6.5e+003  (calc by model)

           Concentration   Half-Life    Emissions
             (percent)        (hr)       (kg/hr)
   Air       4.47            26.7         1000
   Water     28.9            360          1000
   Soil      63.7            360          1000
   Sediment  2.87            1.44e+003    0


              Fugacity    Reaction    Advection   Reaction
Advection
               (atm)       (kg/hr)      (kg/hr)    (percent)
(percent)
   Air       5.21e-011    941         363         31.4
12.1
   Water     1.91e-009    453         235         15.1
7.84
   Soil      3.02e-010    996         0           33.2
```

```
0
   Sediment  6.08e-010    11.2        0.466       0.373
0.0155

   Persistence Time: 271 hr
   Reaction Time:    338 hr
   Advection Time:   1.36e+003 hr
   Percent Reacted:  80
   Percent Advected: 20

   Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
      Air:      26.74
      Water:    360
      Soil:     360
      Sediment: 1440
        Biowin estimate: 2.809  (weeks       )

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004
```

Reliability : (2) valid with restrictions
Estimated values based on model recommended by US EPA.
Flag : Critical study for SIDS endpoint
26.11.2002

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 3mg/l related to Test substance
related to
Contact time : 20 weeks
Degradation : 51 - 94 % after 7 day
Result : Study showed that DPO was susceptible to primary biodegradation)
Deg. Product :
Method : other
Year : 1983
GLP : no
Test substance : other TS
Method : Biodegradation screening was carried out using a semi-continuous activated sludge (SCAS) procedure for primary biodegradation. Study design was patterned after the standard method as found in JAOCS 42:986 (1965) and JAOCS 46:432 (1969). Mixed liquor from a local domestic waste treatment plant was charged to a magnetically-stirred vessel of 1.5 L capacity. Means for aeration and liquid sampling were provided. The SCAS unit was operated on a 24-h cycle. At the beginning of each cycle, DPO at a rate of 3 (second through sixth week), 10 (seventh through fourteenth week) or 50 (fifteenth through twentieth test week) mg/L and sewage were added to the mixed liquor. Aeration was maintained until the end of the cycle, at which time the sludge was settled and supernatant drained. The cycle was then re-initiated by the addition of tap water, sewage and test material. Primary biodegradation was determined during

one cycle each week by analyzing 50 ml mixed liquor samples drawn at the end of the cycle. The test was terminated after 20 weeks. Volatility loss was monitored for one complete cycle. DPO was extracted from the mixed liquor sample using hexane, and analyzed by GC fit with an FID detector. Mean recovery of earlier spiking samples was 93%.

Result : Nearly complete disappearance (>94%) was noted at the lowest feed level tested. At the intermediate feed level, the disappearance rate dropped to 54 % and to 51% at the highest feed level in a concentration dependent manner. Mean volatility losses for DPO were 28%.

Test substance : unspecified but likely commercial grade with purity > 99%

Reliability : (2) valid with restrictions
Used well established methodology for determination of this endpoint. Results were consistent with other biodegradation studies cited in the EUB IUCLID for DPO (2000).

Flag : Critical study for SIDS endpoint

25.11.2002 (9)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Type : static

Species : *Oncorhynchus mykiss* (Fish, fresh water)

Exposure period : 96 hour(s)

Unit : ug/l (micrograms/L or ppb)

Analytical monitoring : Yes, fish tissue and aquarium water were both analyzed for ^{14}C activity

Exposure Concentrations : Forty fish exposed to 2.8 ug/L, in triplicate
Forty fish exposed to 0.4 ug/L, in triplicate
Forty control fish, in triplicate

Method : other

Year : 1973

GLP : No

Test substance : ^{14}C-radiolabeled diphenyl oxide (DPO); 50 uCi/mg specific activity; >99% pure

Test organism : 10-13 cm in total length and 8-10 grams in weight

Method : Rainbow trout (*Oncorhynchus mykiss*) were placed in a flow-through exposure to ^{14}C-radiolabeled DPO for 96 hours and then transferred to fresh water for a 96 hour clearance period. Fish were exposed separately to either a mean, measured concentration of 0.4 ug/L or 2.8 ug/L. The flow-through system provided a turnover rate of approximately 1 L/g-fish/day and triplicate 12-L aquaria were used, with a total of forty fish for each exposure and control.

To experimentally confirm the steady-state concentrations in each short-term, 96-hour exposure, longer term, 42-day exposures (plus a control) were also conducted, at measured ^{14}C-radiolabeled DPO dose levels of 0.28 and 1.7 ug/L.

Aliquots (2 mL) of exposure water were analyzed for total ^{14}C activity by direct liquid scintillation analysis, with proper correction for quenching. Fish muscle tissue was analyzed for total combustible ^{14}C activity using a Beckman Biological Material Oxidizer. Whole fish tissue was also extracted with diethyl ether of potassium hydroxide digests and analyzed by gas chromatography/mass spectrometry (GC/MS) for DPO and metabolites.

Kinetic rate constants were calculated and optimized using a non-linear least squares program. The bioconcentration factor (BCF) was calculated

from the values of the uptake (K_1) and clearance (k_2) rate constants, using a simple two-compartment model (BCF = K_1/ k_2).

Result : A mean uptake rate constant (K_1) of 5.5 (+/- 0.5) mL/g/hr and a mean clearance rate constant (k_2) of 0.028 (+/- 0.003) hr^{-1} were measured from the two exposure concentrations, yielding an average steady-state BCF value in trout muscle of 196 (+/- 26) for DPO. The measured elimination rate constant produces a pseudo first-order elimination half-life for DPO from rainbow trout tissue of 25 hours.

The measured lipid content of the fish used in this study was 1.0-1.5% by weight.

These short-term exposure rate constants were confirmed by good agreement of estimated steady-state fish residues with measured ^{14}C residues in fish in the longer-term, 42-day exposure studies.
Within the limits of analytical detection, there did not appear to be any metabolites of DPO observed in the extracted whole fish tissue. As a result, the uptake, storage, and clearance of ^{14}C-DPO was considered to be the parent compound.

In summary, the relatively low steady-state BCF value of DPO in rainbow trout tissue is explained by the biological half-life of ~25 hours for elimination of DPO from trout muscle. Concomitant longer-term exposures conducted along side the 96-hr experiments in this study suggest that determination of uptake and clearance rate constants from short-term studies are consistent with rate constants from steady-state conditions in longer-term exposures.

Reliability : (2) valid with restrictions
Study is generally consistent with OECD guidance.

Flag : Supplemental study for SIDS endpoint

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 4.2
Method	:	other
Year	:	1980
GLP	:	yes
Test substance	:	other TS
Method	:	Followed methodology outlined in Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, US EPA Ecolog. Res. Series, 1975. Ten fish (average weight of 0.31 g and mean length of 29.2 mm obtained from Beitey Resort, Valley WA, USA), fasted 48 hr before treatment, were tested for up to 96-h at 5 concentrations of DPO in acetone between 1 and 10 mg/L. Both a positive control (Antimycin A) and a solvent control were used. Temperature was maintained at 12 deg. C. Fish were observed for signs of toxicity and mortality at least daily. LC50 values were calculated using a computerized LC50 program developed by Stephen et al, 1978, US EPA Duluth, MI). Tests were conducted in 5 gal glass vessels containing 15 L. lab well water and held at a constant temp. of 12 deg. C.
Result	:	96-h LC50 (CI 95%) = 4.2 (3.2-5.6) mg/L; the 48-Hr LC50 (plus CI) was: 6.0 (4.7-7.8). The dOxy was 60-100%, the pH constant in all groups at 7.8, and all groups had a NH3 level <0.28 ppm (well below the toxic limit). Water quality indices at study start were found to be: dO2 = 9.3 mg/L., pH = 8.2; Hardness (CaCO3) = 225 ppm, alkalinity (CaCO3) = 368 ppm. Total ammonia was < 0.05 in all test groups. No deaths occurred in either control group or in the 1, 1.8 or 3.2 mg DPO /ml/day test groups throughout the study. Deaths occurred at the 5.6 and 10 mg/L concentrations at 24, 48 and 96-h, as follows: 0 %,. 50%, 100%, respectively at 5.6 mg/L and 50%, 90%, and 100%, respectively, at 10 mg/L. Loss of equilibrium and surfacing were observed at the two higher test levels.
Test substance	:	Unspecified but likely commercial grade with purity >99%.
Reliability	:	(2) valid with restrictions Study is consistent with OECD guidance and was conducted under GLPs.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (5)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	= 10
LC50	:	= 13
Method	:	other
Year	:	1980
GLP	:	yes
Test substance	:	other TS
Method	:	Followed design in Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, US EPA Ecolog Res Series, 1975. Groups of 10 fathead minnows (mean weight of 0.24 g; mean length of 25.1 mm, obtained from Fattig Fish Hatchery, Brady, NE, USA) were tested for up to 96-h at 5 DPO (in acetone) test concentrations. Untreated and solvent controls and a positive control (antimycin A) were also employed. Temperature was maintained at 22 deg. C. Studies were

conducted in 5 gal glass jars filled with 15 L well water. Test concentrations had a hardness (CaCo3) of 225 ppm, alkalinity (CaCO3) of 368 ppm, NH3 < 0.28, pH ranging between 7.6-7.7 and dis. Oxygen ranging between 9.0 and 3.0 mg/L. LC50 values and CI were calculated using the method of Stephen et al, 1978. US EPA Environ. Res. Lab, Duluth, MI, USA.

Remark : Dissolved oxygen values in control group was >40 % saturation throughout study. However, in some DPO-treated groups the oxygen level fell below that level during the last 24 hrs of testing. No impact on mortality was observed in this study as there were no additional deaths observed at any test concentration during this period of the study.

Result : 96-h LC50 (95% CI) = 13 (10-18) mg/L; 48-h LC50 (95%CI) = 13 (10-18) mg/L; 24-h LC50 (95% CI) = 34 (18-56) mg/L. Following was the % mortality seen at each test concentration at 24, 48 and 96h respectively: control- 0,0,0; solvent control -0,0,0; 10 mg/L- 0,0,0; 18 mg/L- 0, 100, 100; 32 mg/L- 40, 100, 100; 56 mg/L- 100, 100, 100; 100 mg/L- 100, 100, 100; loss of equilibrium was noted in fish at test concentrations of 18 mg/L and higher. An oily substance was noted at all test levels.

Reliability : (2) valid with restrictions
Well conducted and documented study with a design similar to OECD 203. Study provided as Supplementary, as the previous acute fish study included in this dossier has been used to fulfill this HPV Endpoint.

25.11.2002 (6)

Type :
Species :
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring :
LC50 : = 1.079
Method : other
Year : 2002
GLP :
Test substance :

Method : An acute fish 96-h LC50 was calculated using ECOSAR from the US EPA. The SAR for neutral organics was used. The equation used was Log LC50= -0.94 log Kow + 1.75, which has a Coefficient of Determination (R2) = 0.942 for the training set. The structure was determined from the CAS RN, as stored in the accompanying database of SMILES notations within ECOSAR. Calculations used measured values for MP, water solubility, and Kow.

Test substance : Diphenyl oxide

Reliability : (2) valid with restrictions
Supplemental information using estimation model recommended by US EPA. As this material is an ether, it is expected to be highly stable in water; thus, the value calculated should be representative of the test material modeled.

26.11.2002 (13)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no
NOEC : = 1
EC50 : = 1.7
EC100 : = 10
Method : other
Year : 1980

GLP	:	yes
Test substance	:	other TS
Method	:	Study design followed recommendations from the US EPA Committtee on Methods for Toxicity Testing with Fish, Macroinvertebrates and Amphibians, Ecolog. Res. Series, 1975. Groups of 10 first instar D. magna (inhouse colony) were exposed to one of 5 test concentrations of DPO in acetone ranging in logarithmic series from 1 to 10 mg/l (i.e. 10, 5.6, 3.2, 1.8 and 1 mg/l); both a solvent control and an untreated control were also used. All concentrations were run in duplicate. Each group was placed in a 250 ml glass beaker filled with 200 ml well water, held at 20 degrees C. with 16 hrs artificial light per day @ 50-70 footcandles. Test article was suspended in 1 ml acetone and added to the respective beaker. Daphnia were observed every 24 hrs for morbidity and mortality. Water quality indices (temp., pH, dissolved oxygen) were measured prior to study start and at the end of the study. Water hardness (CaCO3) was 225 ppm. LC50 values (24 and 48 hr) were calculated using the method of Stephen, Busch, Smith, Burke and Anderson, USEPA Duluth Labs computer model, 1978. pH ranged between 8.0-7.8 and dis. Oxygen betwen 9.5-9.4 in all groups.
Result	:	The 48-h LC50 (CI 95%) = 1.7 (1.5-1.9) mg/L. The 24-h LC50 (95% CI) = 2.2 (1.9-2.5) mg/L. The NOEC (48-h) = 10 mg/L. Following are the levels (%) mortality seen in each test concentration at 24-h and 48-h, respectively: control- 0, 0; solvent control - 0, 0; 1 mg/L - 0, 0; 1.8 mg/L - 0, 70; 3.2 mg/L - 35, 95; 5.6 mg/L- 85, 100; 10 mg/L - 100, 100.
Test substance	:	DPO unspecified but likely commercial grade with purity of > 99%.
Reliability	:	(2) valid with restrictions Study design consistant with OECD 202.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (4)

Type	:	other
Species	:	
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	
EC50	:	= 1.346
Method	:	other
Year	:	2002
GLP	:	
Test substance	:	other TS
Method	:	An acute Daphnia 48-h LC50 was calculated using ECOSAR, from the US EPA. The SAR for neutral organics was used. The equation used was Log LC50 = 1.72-0.91 log Kow, which has a Coefficient of Determination (R2) = 0.992 for the training set. The structure was determined from the CAS RN, as stored in the accompanying database of SMILES notations within ECOSAR. Calculations were made using measured values for MP, water solubility, and Kow.
Test substance	:	Diphenyl oxide
Reliability	:	(2) valid with restrictions. Supplemental information provided using estimation model recommended by US EPA. As this material is an ether, it is expected to be highly stable in water; thus, the values calculated should be representative of the test material modeled.

26.11.2002 (13)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	96 hour(s)
Unit	:	mg/l

Analytical monitoring	:	no
EC50	:	= 2.5
Method	:	other
Year	:	1980
GLP	:	yes
Test substance	:	other TS
Method	:	Study procedures followed guidance found in The S. capricornutum Printz Algal Assay Test. Experimental Designs, Application and Data Interpretation. Corvallis, Environmental Research Laboratory, US EPA, 1978. Study designed to measure both decrease of in vivo chlorophyll a and a decrease in cell number over time. Algae was obtained from the US EPA Env. Res. Lab, , Corvallis, OR, USA. A least 2 x 10E4 cells/mL were incubated at 24 deg C with 4000 lux illumination at 5 test concentrations (0.6, 1.2, 2.5, 5, and 10 mg/L). Both an untreated control and a solvent (triethylene glycol) control group were also included in the test. All test concentrations were conducted in triplicate. The test system was 125 ml flasks containing 50 ml test medium, the pH ranged between 7.2-7.6 throughout the study. Chlorophyll measurements were taken using a fluorometer; cells counts were made using a hemacytometer and compound microscope. Data were treated statistically by using the probit method of Finney (1971) followed by linear regression analysis. A probablitity factor of 5% was used.
Result	:	Based on the decrease in chlorophyll the following EC50 values (95%CI) were calculated: 96-h = 2.5 (1.2-5.4) mg/L; at 72-h and 48h = >2.5<5.0 mg/L; at 24-h = > 10 mg/L. Based on the number of decreased cells, the 96-h LC50 (95% CL) = 2.5 (1.2-5.3) mg/L
Test substance	:	DPO unspecified but likely commercial grade with purity of > 99%.
Reliability	:	(2) valid with restrictions GLP conducted study following a regulatory-recommended study design.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (8)

Species	:	other algae
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	= .955
Method	:	other
Year	:	2002
GLP	:	
Test substance	:	other TS
Method	:	An acute green algal 96-h LC50 was calculated using ECOSAR, from the US EPA. The SAR for neutral organics was used. The equation used was Log 96-h EC50 = 1.466-0.885 log Kow, which has a Coefficient of Determination (R2) = 0.91 for the training set. The structure was determined from the CAS RN, as stored in the accompanying database of SMILES notations within ECOSAR. Calculations were made using measured values for MP, water solubility and Kow.
Test substance	:	Diphenyl oxide.
Reliability	:	(2) valid with restrictions Supplemental information using US EPA recommended estimation model. As this material is an ether, it is expected to be highly stable in water. The value calculated should be representative of the test material modeled.

26.11.2002 (13)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	other: undiluted
Value	:	= 2450 mg/kg bw
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	other TS
Method	:	DPO was administered undiluted via single dose gavage to groups of 5 fasted Sprague-Dawley rats (either 2 or 3 males per group; concomitantly, 3 or 2 females per group) per dose group at dosages of 2000, 2510, and 3160 mg/kg. Rats were observed approximately 1 hour after dosing and twice daily over a 14-day observation period for signs of toxicity. Body weights were recorded individually at inception and on test days 7 and 14. All rats found dead or sacrificed by design at the end of the observation period were given a gross necropsy. LD50, CL and slope calculated by the method of deBeer,E. 1945. J. Pharmacol. Experimen. Ther. 85:1. Humidity, temperature and lighting were controlled. Food was administered ad libitum.
Result	:	No deaths (0/5) at 2000 mg/kg; 3/5 dead at 2510 mg/kg and 5/5 dead at 3160 mg/kg. Generalized weakness observed prior to death; necropsy of decedents resulted in identification of liver and lung hyperemia and acute gastrointestinal inflammation. 95% Confidence Limits of 2200-2720 mg/kg
Test substance	:	DPO of >99% purity
Reliability	:	(2) valid with restrictions Study conducted prior to, but consistent with, pending US GLPs 21 CFR

58, and effective 20 June, 1979. The study design used is consistent with guidelines and endpoints listed in OECD Test Guideline 401, although fewer animals were used. Results in this study are consistent with a similar degree of oral toxicity reported in the literature (Weir, 1974. Fd Cosmet Tox 12:707).

Flag : Critical study for SIDS endpoint
25.11.2002 (12)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	oral feed
Exposure period	:	90- days
Frequency of treatment	:	Daily
Post obs. period	:	4-weeks
Doses	:	0, 200, 1000, 5000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	> 5000 ppm
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Method	:	Four groups of Sprague Dawley albino rats (10/sex) were exposed to graded concentrations of 0, 200, 1,000, or 5,000 ppm DPO in the diet for 13 weeks. An additional 10 rats/sex/group were designated as recovery rats and were retained for 4 weeks after the 13-week feeding period and received untreated rodent chow during that latter interval. Test article was prepared neat in a premix and subsequent diets prepared weekly. Analyses were conducted periodically for homogeneity and test article concentration levels. Daily physical exams and clinical observations were performed on each animal. Body weights and food consumption were recorded weekly for each animal. Ophthalmoscopic exams were performed at study start and after 13 weeks on test for all animals. The following clinical exams were performed on each animal prior to necropsy: GLU, CK, ALT, SGPT, AST, SGOT. ALKP, GGT, BUN, CREA, Na, K, Ca, Cl, Phos, TPRO, ALB, TBIL, CHOL,RBC, HGB, MCV, WBC, PLAT, GLOB, A:G ratio,

HCT, MHC, MCHC, urine appearance, volume, Spec. grav., occult blood, protein, pH, ketones, urobilinogen, GLU, BILI, sediments. Complete necropsies were performed on all rats at study termination and a set of 46 tissues collected for microscopic exam. Histopathologic examinations were performed on all animals from the control and HD groups after 13 weeks, as well as lungs, liver, kidneys, and gross lesions from 200 ppm and 1000 ppm animals after 13 weeks. Absolute and relative organ (brain, gonads, heart, kidneys, liver and spleen) weights were recorded at necropsy. Body weights and gains and food consumption and ratio data were evaluated using multivariate repeated-measure analysis of variance while other data were log-transformed and statistically analyzed using both multivariate and univariate two-factor fixed-effect analysis of variance (ANOVA). All comparisons for combined data of sexes were conducted using the Dunnett's test for multiple comparisons. A minimum significance level of $p<0.05$ was used throughout. Gonads of all high dose and control animals were examined microscopically

Remark : Systemic NOEL considered 5000 ppm as findings at 1000/5000 ppm considered palatability induced

Result : Periodic analyses of feed confirmed homogeneity and test article concentration. Dosage determinations: males - 0, 11.7, 60.7 & 301.1 mg/kg/day; females - 0,14.5, 73.9, & 334.8 mg/kg/day. None of the test or recovery animals died during the 13-week feeding or 4-week treatment/recovery periods. No signs of test article-related clinical toxicity were observed during the 13-week treatment period, nor were any adverse signs noted during the recovery period. Mean weekly body weight and food consumption were significantly decreased in 5000 ppm males and females during entire 13-week treatment period. Statistically significant decreases in mean body weight and food consumption also were noted in the 1000 ppm female group during most of the study. These changes were attributable to decreased palatability of test diet, as evidenced by statistically significant increases in food consumption and/or body weight gain and increased food conversion ratios during one or more weeks of recovery. No treatment-related clinical chemistry, urinalysis, or hematology were observed, nor were there ocular manifestations of toxicity. The few statistically significant differences noted in the above parameters were either not dose-related, within range of in-house historical values or occurred only in recovery animals. No absolute organ weight changes attributable to treatment were observed, nor were there any gross lesions or histopathological effects related to treatment, including male and female gonads. The few statistically significant differences in relative weights observed in both sexes in the high dose group and mid dose females were attributed to their substantive decreased body weights seen at termination of treatment and not direct target organ toxicity. No treatment-related gross lesions were observed in this study. No histopathological effects related to DPO-treatment were observed, including male and female gonads.

Test substance : Commercial grade DPO with presumed purity > 98%.

Reliability : (1) valid without restriction
Study conducted under GLPs and consistent with OECD Test Guideline 408.

Flag : Critical study for SIDS endpoint

25.11.2002 (3)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test

System of testing : Spot test and Plate Incorporation Assay

Concentration : ST-10 mg/plate; PIA-0.1, 1, 10, 33, 100 and 500 ug/plate

Cycotoxic conc. : 1 mg/plate w & w/o activation in Spot test; lower levels in PIA

Metabolic activation : with and without

Result : negative

Method	:	other
Year	:	1978
GLP	:	no
Test substance	:	other TS
Method	:	Methodology employed prior to codification of, but consistent with OECD guideline 471. Media and handling procedures and preparation of liver microsomal fractions (S-9) followed the procedure outlined in Ames et al. Mut. Res. 31:347-364. Salmonella tester strains used were TA1535, TA1537, TA98, and TA100. DMSO was used as a solvent. Toxicity test using TA100 conducted at 0.1, 1, 3 and 10 mg/plate with and without activation. A toxic response was considered a concentration which eliminated background lawn or reduced it to individual colonies. Plate Incorporation assay run in triplicate. A Spot Test was conducted using all four Salmonella tester strains prior to conduct of the plate incorporation assay, where it was applied directly to the center of the plate on sterile paper discs. DPO was evaluated at a maximum level of 10 mg/plate, with and without mouse and rat microsomal preparations. After 48 hours incubation, the number of colonies on the plate and pattern of colonies were visually examined. A positive response was judged by formation of a halo of revertant colonies around the plate center. A Plate Incorporation Assay was performed using 6 concentrations of DPO in DMSO resulting in levels of 0.1, 1, 10, 33, 100 and 500 ug DPO/plate. Tests were performed by adding bacterial suspensions, test sample and metabolic activation (S-9) mix (if appropriate) to histidine-biotin top agar, rapidly mixed and poured onto minimal glucose plates. Colonies were counted after 48-hours incubation. Each concentration was run in triplicate. Tester strains TA1535, TA 1537, TA 98, and TA 100 each with and without metabolic activation, were assayed at each DPO concentration. The highest concentration tested corresponded to one-half the lowest concentration giving severe toxicity in the Toxicity Test. Appropriate solvent and negative controls were run. Following were used as positive controls: TA1535 - $NaNO_2$ and Tris (2,3-dibromopropyl) phosphate for -/+ S-9, respectively; TA1537 - 9-aminoacridine and 2-aminoanthracene for -/+ S-9, respectively; TA98 - 4-nitroquinoline-N-oxide and 2-acetamidofluorene for -/+ S-9, respectively; and TA100 - 4-nitroquinoline-N-oxide and benzo(a)pyrene for -/+ S-9, respectively. S9 co-factor was prepared according to Mut. Res. 31:347-64. Revertants/plate were transformed to log 10 and within pooled variance for calculation; comparisons were made via t-test ($p<0.01$).
Result	:	Levels of 1 mg/plate w/wo activation produced severe toxicity; No mutagenic activity at max. conc. used of 10 mg/plate in all 4 tester strains in the Spot Test; In the Plate Incorporation Assay, toxicity was observed in strains TA98 and TA100 at 500 ug/plate and 33 ug/plate and higher for TA1535 and TA1537. No mutagenic activity was detected towards any of the 4 tester strains, with or without metabolic activiation.
Test substance	:	Purity of test sample was > 99%
Reliability	:	(2) valid with restrictions Study conducted prior to , but consistent with pending US GLP 21 CFR 58, effective 20, June 1979. Results are consistent with those reported from NTP program and summarized in Haworth et al.1983. Environ. Mutagen. 5:3-142
Flag	:	Critical study for SIDS endpoint

25.11.2002 (10)

Type	:	Chromosomal aberration test
System of testing	:	CHO Cells
Concentration	:	10,50,100 &150 ug/ml (no S-9); 5,30,50 ug/ml (with S-9)
Cycotoxic conc.	:	150 ug/ml (with S-9)
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year	:	1978

GLP	:	yes
Test substance	:	other TS
Method	:	Preliminary cytotoxicity study used 5,50,100,125,500,750,1000,2500,5000 ug/ml with and without metabolic activation. In this study, cells were exposed to the test article for 5 hours, washed, and incubated in fresh BrdU-containing medium for an additional 27 hours. To arrest cells in metaphase, the flasks contained Colcemid for the last 2-3 hours of incubation. Cells were then harvested, and Giesma-stained chromosome preparations were prepared and examined. Cell kinetics were based on the number of cell cycles completed after exposure to DPO using 100 metaphase cells for the evaluation. In the definitive study, DPO was incubated in CHO cell cultures, both with and without metabolic activation. Each evaluation was performed with cells from duplicate flasks. Based on the preliminary study results of proliferation kinetics and cytotoxic effects, DPO was evaluated with and without metabolic activation at optimized concentrations with 5 hour exposure followed by washing and then 18 hrs of additional incubation; After cell harvest, Giesma-stained chromosomal preparations were prepared on slides and at least 50 cells/flask (100 cells/dosage) were evaluated. All slides were scored blind and statistically analyzed using a "t"-test to compare pairwise each treatment group with the control group using aberrants per cell. The proportion of aberrant metaphases were analyzed using Chi-square analysis. Significance was generally determined at the $p<0.05$ probability level. Dosing solutions prepared in acetone. N-nitrosodimethylamine and MNNG, used as positive controls.
Result	:	Preliminary Study - Cytotoxicity seen at dosages above 500 ug/ml without S-9 and above 250 ug/ml with S-9; cell proliferation times increased at and above 250 ug/ml without S-9 and at and above 50 ug/ml with S-9; Definitive Study - DPO concentrations of 10, 50, 100 and 150 ug/ml (without S-9) and 5, 30 and 50 ug/ml (with S-9) were used. The 150 ug/ml concentration was cytotoxic. DPO did not produce significant increases in the percentage of structural aberrations per cell at any treatment concentration. Both positive control materials elicited the expected increases in aberrations, confirming the sensitivity of the assay to known clastogens.
Test substance	:	DPO with purity > 99%
Reliability	:	(1) valid without restriction GLP study which meets OECD Guideline 473 parameters.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (11)

5.6 GENETIC TOXICITY 'IN VITRO'

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Gestation days 6-15
Frequency of treatment	:	Daily 1X

Duration of test	:	Through gestation day 15
Doses	:	50, 200, 500 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	>= 50 mg/kg bw
NOAEL Teratogen	:	>= 500 mg/kg bw
NOAEL Embryotoxicity	:	>= 500 mg/kg bw
NOAEL Fetotoxicity	:	>= 500 - mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1986
GLP	:	yes
Test substance	:	other TS
Method	:	DPO was mixed with corn oil and administered to groups comprised of 24 mated Charles River CD female rats each at dosage levels of 0, 50, 200 or 500 mg/kg/d. Single oral daily dosages were administered at a volume of 5 ml/kg by gavage, on gestation days 6-15. Approximately 1/2 of the fetuses in each litter were processed for soft-tissue evaluations while the other half for skeletal evaluations. Statistical evaluation of equality of means was made by the appropriate one-way analysis of variance technique (ANOVA) for parametric procedures and Kruskal-Wallis test for nonparametric procedures were used after applying Bartlett's test for determination of equal variance. Statistical tests for trend, using either standard regression techniques (parametric cases) or Jonckheere's test in nonparametric cases. Levels of statistical significance used were either $p<0.05$ or $p<0.01$.
Result	:	2 deaths occurred at 500 mg/kg. Statistically reduced maternal weight gain and food consumption were observed at 200 and 500 mg/kg/d. Excessive alopecia, salivation and/or anogenital staining was observed but no pattern of treatment relationship could be determined. No effects observed on fetal resorptions, fetal viability, postimplantation loss or total implantations. Mean litter weights in treated and control groups were similar. No significant increases were observed in incidence of malformations or variations at any treatment level.
Test substance	:	73.5% DPO & 26.5% biphenyl mixed in corn oil at volume of 5 ml/kg
Reliability	:	(1) valid without restriction GLP-conducted study which meets OECD Test Guideline 414. Lack of any developmental toxicity observed in this study obviates any concern of differentiating findings between either of the major components in this test mixture.
Flag	:	Critical study for SIDS endpoint

25.11.2002 (7)

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(1) AOP, v. 1.8. 1997. Syracuse Research Corp., Syracuse, NY.

(2) Banerjee, S, Yalkowski, SH and SC Valvani. 1980. Environ Sci Technol 14:1227 (measured value)

(3) IITRI Project No. L8100 (Study no. 1482) Thirteen-Week Oral (diet) Toxicity Study of Diphenyl Ether in Rats; also published in The Toxicologist 12 (1):117 (1992);

(4) Solutia study no. AB-80-242. Acute Toxicity of DPO (Diphenyl Oxide) to Daphnia magna.

(5) Solutia study no. AB-80-243. Acute Toxicity of DPO to Rainbow Trout.

(6) Solutia study no. AB-80-244. Acute Toxicity of Diphenyl Oxide to Fathead Minnows.

(7) Solutia study no. BD-86-379. A Developmental Toxicity Study in Rats with THERMINOL VP-1 Heat Transfer Fluid.

(8) Solutia study no. BN-80-241. Toxicity of DPO (Diphenyl oxide) to the freshwater alga S. capricornutum.

(9) Solutia study no. ES-83-SS-23. Biodegradaton screening of biphenyl, diphenyl oxide, and TERMINOL VP-1.

(10) Solutia Study No. LF-78-168. Salmonella Mutagenicity Assay of Diphenyl Oxide.

(11) Solutia Study No. PK-86-423; In Vitro Chromosome Aberration Analysis in Chinese Hamster Ovary (CHO) Cells. EPA OTS Doc. 86-890000343.

(12) Solutia Study No. YO-77-72. Toxicity Studies on Diphenyl oxide. EPA TSCATS no. 86-8900000346

(13) US EPA ECOSAR model, v. 0.99f.

(14) Vershueren (ed.). 1983. Handbook on Environmental Data of Organic Compounds. 2nd edit. Van Nostrand Reinhold Co, NY.

7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT